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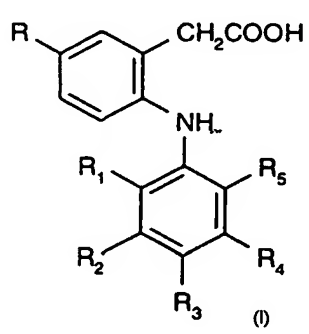
(54) Title: METHODS AND COMPOSITIONS FOR TREATMENT OF CANCER PAIN



(I)

(57) Abstract: The invention provides a method of treating cancer pain, e.g. bone cancer pain, in a subject in need of such treatment which comprises administering to the subject an effective amount of a COX-2 inhibitor; advantageously a compound of formula (I); wherein R, R_1 R_2, R_3, R_4, and R_5 are as defined; a pharmaceutically acceptable salts thereof; or a pharmaceutically acceptable prodrug ester thereof.

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METHODS AND COMPOSITIONS FOR TREATMENT OF CANCER PAIN

This invention relates to selective cyclooxygenase-2 inhibitors (COX-2 Inhibitors), in particular to the use of COX-2 inhibitors in the treatment of cancer pain, especially bone cancer pain.

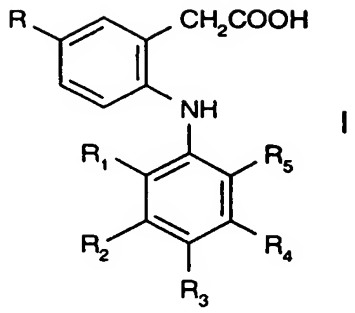
COX-2 inhibitors and their use as non-steroidal anti-inflammatory drugs (NSAIDs) for the treatment of inflammatory diseases and pain are well known in the art. Further it has been proposed (WO 99/11605) that COX-2 inhibitors may be useful for treatment of neoplasia particularly neoplasias that produce prostaglandins or express cyclooxygenase, including both benign and cancerous tumors, growths and polyps.

It has now been found that certain COX-2 inhibitors, in particular 5-alkyl substituted 2-arylaminophenylacetic acid derivative COX-2 inhibitors, have desirable properties for use in the treatment of Cancer pain, in particular bone cancer pain.

Accordingly the invention provides a method of treating cancer pain in a subject in need of such treatment, which comprises administering to the subject an effective amount of a COX-2 inhibitor.

Suitable COX-2 inhibitors for use in the invention may include the following compounds or derivatives thereof or a pharmaceutically acceptable salt thereof, or any hydrate thereof: rofecoxib, etoricoxib, celecoxib, valdecoxib, parecoxib, or a 5-alkyl-2-arylaminophenylacetic acid derivative COX-2 inhibitor.

In preferred embodiments the invention provides a method of treating cancer pain in a subject in need of such treatment which comprises administering to the subject an effective amount of a COX-2 inhibitor of formula I



I

wherein R is methyl or ethyl;

R_1 is chloro or fluoro;

R_2 is hydrogen or fluoro;

R_3 is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxy;

R_4 is hydrogen or fluoro; and

R_5 is chloro, fluoro, trifluoromethyl or methyl;

a pharmaceutically acceptable salt thereof; or

a pharmaceutically acceptable prodrug ester thereof.

Further the invention provides the use of a compound of formula I (or pharmaceutically acceptable salt or prodrug ester thereof) as defined above for the preparation of a medicament, for use in the treatment of cancer pain.

In a further aspect the invention provides use of a Cox-2 inhibitor, advantageously a compound of formula I (or pharmaceutically acceptable salt or prodrug ester thereof) as defined above for the treatment of cancer pain.

In a yet further aspect the invention provides cancer pain treatment agent comprising a Cox-2 inhibitor, advantageously a compound of formula I (or pharmaceutically acceptable salt or prodrug ester thereof) as defined above as active ingredient.

In a still yet further aspect the invention provides a package comprising a Cox-2 inhibitor, advantageously a compound of formula I (or pharmaceutically acceptable salt or

prodrug ester thereof) as defined above together with instructions for use in the treatment of cancer pain.

The compounds of formula I may be used for treatment of cancer pain in general. In a particularly preferred embodiment the compounds of formula I are used for the treatment of bone cancer pain including pain associated with primary bone cancer such osteosarcoma, and also pain associated with bone metastases of primary cancers such as breast, colon, lung, prostate and other cancers, e.g. multiple myeloma.

In the present description the terms "treatment" or "treat" refer to both prophylactic or preventative treatment as well as curative or disease modifying treatment, including treatment of patients at risk of contracting the disease or suspected to have contracted the disease as well as patients who are ill or have been diagnosed as suffering from a disease or medical condition.

Particularly preferred compounds of formula I are those wherein R is methyl or ethyl; R_1 is chloro or fluoro; R_2 is hydrogen; R_3 is hydrogen, fluoro, chloro, methyl or hydroxy; R_4 is hydrogen; and R_5 is chloro, fluoro or methyl; pharmaceutically acceptable salts thereof; and pharmaceutically acceptable esters thereof.

A particularly preferred embodiment relates to the compounds of formula I wherein R is methyl or ethyl; R_1 is fluoro; R_2 is hydrogen; R_3 is hydrogen, fluoro or hydroxy; R_4 is hydrogen; and R_5 is chloro; pharmaceutically acceptable salts thereof; and pharmaceutically acceptable prodrug esters thereof.

Another particularly preferred embodiment of the invention relates to compounds of formula I wherein R is ethyl or methyl; R_1 is fluoro; R_2 is hydrogen or fluoro; R_3 is hydrogen, fluoro, ethoxy or hydroxy; R_4 is hydrogen or fluoro; and R_5 is chloro, fluoro or methyl; pharmaceutically acceptable salts thereof; and pharmaceutically acceptable prodrug esters thereof.

Further are said compounds wherein R is methyl or ethyl; R_1 is fluoro; R_2-R_4 are hydrogen or fluoro; and R_5 is chloro or fluoro; pharmaceutically acceptable salts thereof; and pharmaceutically acceptable prodrug esters thereof.

A further embodiment of the invention relates to the compounds of formula I wherein R is methyl or ethyl; R_1 is fluoro; R_2 is fluoro; R_3 is hydrogen, ethoxy or hydroxy; R_4 is fluoro; and R_5 is fluoro; pharmaceutically acceptable salts thereof; and pharmaceutically acceptable prodrug esters thereof.

Another embodiment of the invention relates to the compounds of formula I wherein R is methyl; R_1 is fluoro; R_2 is hydrogen; R_3 is hydrogen or fluoro; R_4 is hydrogen; and R_5 is chloro; pharmaceutically acceptable salts thereof; and pharmaceutically acceptable prodrug esters thereof.

Particularly preferred embodiments of the invention relate to compounds of formula I

(a) wherein R is methyl; R_1 is fluoro; R_2 is hydrogen; R_3 is hydrogen; R_4 is hydrogen; and R_5 is chloro; pharmaceutically acceptable salts thereof; and pharmaceutically acceptable prodrug esters thereof;

(b) wherein R is methyl; R_1 is fluoro; R_2 is hydrogen; R_3 is fluoro; R_4 is hydrogen; and R_5 is chloro; pharmaceutically acceptable salts thereof; and pharmaceutically acceptable prodrug esters thereof;

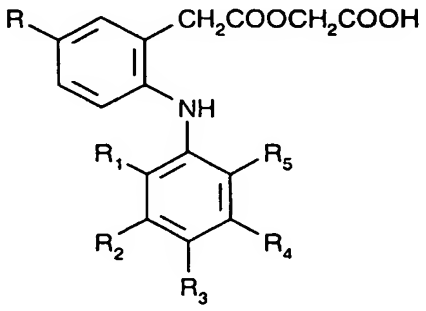
(c) wherein R is ethyl; R_1 is fluoro; R_2 is fluoro; R_3 is hydrogen; R_4 is fluoro; and R_5 is fluoro; pharmaceutically acceptable salts thereof; and pharmaceutically acceptable prodrug esters thereof; and

(d) wherein R is ethyl; R_1 is chloro; R_2 is hydrogen; R_3 is chloro; R_4 is hydrogen; and R_5 is methyl; pharmaceutically acceptable salts thereof; and pharmaceutically acceptable prodrug esters thereof.

Most preferably 5-methyl-2-(2'-chloro-6'-fluoroanilino)-phenylacetic acid or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable prodrug thereof is used as the COX-2 inhibitor of the invention.

Pharmacologically acceptable salts of the compounds of formula I are preferably salts with bases, conveniently metal salts derived from groups Ia, Ib, IIa and IIb of the Periodic Table of the Elements, including alkali metal salts, e.g. potassium and especially sodium salts, or alkaline earth metal salts, preferably calcium or magnesium salts, and also ammonium salts with ammonia or organic amines.

Pharmaceutically acceptable prodrug esters of the compounds of formula I are ester derivatives which are convertible by solvolysis or under physiological conditions to the free carboxylic acids of formula I. Such esters are e.g. lower alkyl esters (such as the methyl or ethyl ester), carboxy-lower alkyl esters such as the carboxymethyl ester, nitrooxy-lower alkyl esters (such as the 4-nitrooxybutyl ester), and the like. Preferred prodrugs are the compounds of formula Ia



(Ia)

wherein R and R_1.R_5 have meaning as defined hereinabove for compounds of formula I; and pharmaceutically acceptable salts thereof.

Compounds of formula I and Ia and their synthesis are described in published international patent applications Nos. WO 99/11605 and WO 01/23346, the teachings of which are incorporated herein by reference.

It has been further discovered in accordance with the present invention that compounds of formual I (and esters and prodrugs thereof), in particular the compound 5-methyl-2-(2'-chloro-6'-fluoroanilino)-phenylacetic acid or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable prodrug thereof, inhibit the radiologically observed structural changes in an animal model of bone cancer pain.

Thus in a yet further embodiment the invention includes a method for the inhibition of bone loss, advantageously in cancer, which comprises administering an effective amount of a COX-2 inhibitor of formula I (or an ester or prodrug thereof) as defined above to the subject in need of such treatment.

The Agents of the Invention, i.e. the COX-2 inhibitors of formula I and pharmaceutically acceptable salts and esters thereof , are preferably used in the form of pharmaceutical preparations that contain the relevant therapeutically effective amount of active ingredient optionally together with or in admixture with inorganic or organic, solid or liquid, pharmaceutically acceptable carriers which are suitable for administration.

The COX-2 pharmaceutical compositions may be, for example, compositions for enteral, such as oral, rectal, aerosol inhalation or nasal administration; compositions for parenteral, such as intravenous or subcutaneous administration; compositions for transdermal administration (e.g. passive or iontophoretic); or compositions for topical adminstration.

Preferably, the COX-2 pharmaceutical compositions are adapted to oral or parenteral (especially oral) administration. Intravenous and oral, first and foremost oral, adminstration is considered to be of particular importance. Preferably the COX-2 inhibitor active ingredient is in oral form.

The particular mode of administration and the dosage may be selected by the attending physician taking into account the particulars of the patient, especially age, weight, life style, activity level, etc .

The dosage of the Agents of the Invention may depend on various factors, such as effectiveness and duration of action of the active ingredient, mode of administration, warm-blooded species, and/or sex, age, weight and individual condition of the warm-blooded animal.

More particularly, the pharmaceutical compositions comprise an effective cyclooxygenase-2 inhibiting amount of COX-2 inhibitor or compound of formula I which is substantially free of cyclooxygenase-1 inhibiting activity and of side effects attributed thereto, when used therapeutically.

The compounds of formula I (and salts and esters thereof) are useful in the manufacture of pharmaceutical compositions comprising an effective amount thereof in conjunction or admixture with excipients or carriers suitable for either enteral or parenteral application. Preferred are tablets and gelatin capsules comprising the active ingredient together with a) diluents, e.g. lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine; b) lubricants, e.g. silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also c) binders e.g. magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and or polyvinylpyrrolidone; if desired d) disintegrants, e.g. starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or e) absorbents, colorants, flavors and sweeteners. Injectable compositions are preferably aqueous isotonic solutions or suspensions, and suppositories are advantageously prepared from fatty emulsions or suspensions. Said compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they may also contain other therapeutically valuable substances. Said compositions are prepared according to conventional mixing, granulating or coating

methods, respectively, and contain about 0.1 to 80%, preferably about 1 to 60% or more, of the active ingredient.

Tablets may be either film coated or enteric coated according to methods known in the art.

Suitable formulations for transdermal application include an effective amount of a compound of the invention with carrier. Advantageous carriers include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. For example, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound of the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

Suitable formulations for topical application, e.g. to the skin and eyes, include aqueous solutions, suspensions, ointments, creams, gels or sprayable formulations, for example, for delivery by aerosol or the like. Such topical delivery systems will in particular be appropriate for dermal application, e.g. for the treatment of skin cancer, for example, for prophylactic use in creams, lotions sprays and the like

The dosage of COX-2 inhibitor administered is dependent on the species of warm-blooded animal (mammal), the body weight, age and individual condition, and on the form of administration. A unit dosage for oral administration to a mammal of about 50 to 70 kg may contain between about 5 and 1500 mg, e.g. from 100-1000 mg, preferably 200-800 mg of the active ingredient.

COX-2 inhibitor formulations in single dose unit form contain preferably from about 1% to about 90%, and formulations not in single dose unit form contain preferably from about 0.1% to about 20%, of the active ingredient. Single dose unit forms such as capsules, tablets or dragées contain e.g. from about 1mg to about 1000mg of the active ingredient.

COX-2 inhibitor pharmaceutical preparations for enteral and parenteral administration are, for example, those in dosage unit forms, such as dragées, tablets or capsules and also ampoules. They are prepared in a manner known *per se*, for example by means of conventional mixing, granulating, confectioning, dissolving or lyophilising processes. For example, pharmaceutical preparations for oral administration can be obtained by combining the active ingredient with solid carriers, where appropriate granulating a resulting mixture, and processing the mixture or granulate, if desired or necessary after the addition of suitable adjuncts, into tablets or dragée cores.

Parenteral formulations are especially injectable fluids that are effective in various manners, such as intravenously, intramuscularly, intraperitoneally, intranasally, intradermally or subcutaneously. Such fluids are preferably isotonic aqueous solutions or suspensions which can be prepared before use, for example from lyophilised preparations which contain the active ingredient alone or together with a pharmaceutically acceptable carrier. The pharmaceutical preparations may be sterilised and/or contain adjuncts, for example preservatives, stabilisers, wetting agents and/or emulsifiers, solubilisers, salts for regulating the osmotic pressure and/or buffers.

The following examples are intended to illustrate the invention and are not to be construed as being limitations thereon.

EXAMPLES

A. Formulation Examples

Example 1

Table 1

Ingredient	Amount per 200 mg tablet batch (kg)
Core	
Granulation	
5-methyl-2-(2'-chloro-6'-fluoroanilino)phenylacetic acid drug substance	50**
Microcrystalline cellulose, NF (PH 101)	12.85
Lactose monohydrate, NF	11.65
Croscarmellose sodium, NF	1
Povidone, USP	4
Titanium dioxide, USP	2
Water, purified ***, USP	20.375
Extra-granular Phase	
Microcrystalline cellulose, NF (PH 102)	13
Croscarmellose sodium, NF	3
Titanium dioxide, USP	2
Magnesium stearate, NF	0.5
Coating	
Opadry white	2.801 ****
Opadry yellow	2.0 ****
Opadry red	0.4 ****
Opadry black	0.0504 ****
Water, purified ***, USP	29.758 ****

** The weight of drug substance is taken with reference to the dried substance (100 per cent) on the basis of the assay value (factorization). The difference in weight is adjusted by the amount of microcrystalline cellulose used.

*** Removed during processing.

**** Includes a 50 % excess for loss during the coating process.

Table 1, above, sets out the formula for a batch of approximately 250,000 immediate release film-coated tablets of 5-methyl-2-(2'-chloro-6'-fluoroanilino)-phenylacetic acid. To make the tablets, titanium dioxide is dispersed in water, followed by the addition of povidone and mixing for 20 minutes to make a povidone/titanium dioxide suspension. The drug substance, lactose, microcrystalline cellulose, and croscarmellose are mixed in a high shear mixer (e.g., a Collette Gral) for 5 minutes to form a drug mixture. The drug mixture is granulated in the high shear mixer with the povidone/titanium dioxide suspension. The suspension is pumped at a rate of 3 kg/min into the drug mixture. The resulting mixture is mixed an additional 90 seconds after all the suspension is added. The wet granulation is dried in a fluid bed dryer, using an inlet air temperature of 50 °C. The residual water target is 3.5 % (with a permissible range of 2.5 – 4.5 %). The dried granulation is passed through a screen using a mill (oscillator) and a 30 mesh screen. The previous steps are repeated to make a second granulation.

The extra-granular phase titanium dioxide is passed through a 60 mesh hand screen. The dry granulations are mixed with the extra-granular phase microcrystalline cellulose, croscarmellose sodium and titanium dioxide in a twin shell mixer for 300 revolutions to form a penultimate mixture. Magnesium stearate is passed through a 60 mesh hand screen and is mixed with the penultimate mixture in a twin shell mixer for 50 revolutions to form a tableting mixture. The tableting mixture is pressed into tablets using a tablet press and oval punches.

The coating powders (Opadry) are mixed with purified water to make a 15 % w/w coating suspension. The tablets are film coated with the coating suspension in a coating pan using 60 °C to 75 °C inlet air temperature.

Table 2 sets out the contents of a 200 mg 5-methyl-2-(2'-chloro-6'-fluoroanilino)phenylacetic acid film-coated tablet.

Table 2

Ingredient	Theoretical amount [mg]	Function
Core		
5-methyl-2-(2'-chloro-6'-fluoroanilino)phenylacetic acid drug substance	200	Active substance
Microcrystalline cellulose (PH 101)	51.4	Filler
Lactose	46.6	Filler
Povidone	16	Binder
Titanium dioxide	8	Color
Croscarmellose sodium	4	Disintegrant
Water, purified *	Q.S.	Granulating liquid
Extragranular phase		
Microcrystalline cellulose (PH 102)	52	Filler
Croscarmellose sodium	12	Disintegrant
Titanium dioxide	8	Color
Magnesium stearate	2	Lubricant
Core weight	**400**	
Coating		
Opadry white (00F18296)	7.4676	Color
Opadry yellow (00F12951)	5.3312	Color
Opadry red (00F15613)	1.0668	Color
Opadry black (00F17713)	0.1344	Color

Ingredient	Theoretical amount [mg]	Function
Water, purified *	Q.S.	Coating solvent
Total weight	**414**	

* removed during processing

In addition, the tablet formulations may contain 5-methyl-2-(2'-chloro-6'-fluoroanilino)benzyl alcohol and/or 5-methyl-2-(2'-chloro-6'-fluoroanilino)benzoic acid in an amount between about 0.01 and 2% by weight, more specifically between about 0.1 and 1.

Example 2

Wet granulated tablet composition

Amount per tablet		Ingredient
25	mg	COX-2 inhibitor
79.7	mg	Microcrystalline cellulose
79.7	mg	Lactose monohydrate
6	mg	Hydroxypropyl cellulose
8	mg	Croscarmellose sodium
0.6	mg	Iron oxide
1	mg	Magnesium stearate

Tablet dose strengths of between 5 and 125 mg can be accomodated by varying total weight, and the ratio of the first three ingredients. Generally it is preferable to maintain a 1:1 ratio for microcrystalline cellulose: lactose monohydrate.

Example 3

Directly compressed tablet composition

Amount per tablet	Ingredient

25	mg	COX-2 inhibitor
106.9	mg	Microcrystalline cellulose
106.9	mg	Lactose anhydrate
7.5	mg	Croscarmellose sodium
3.7	mg	Magnesium stearate

Tablet dose strengths of between 5 and 125 mg can be accomodated by varying total tablet weight, and the ratio of the first three ingredients. Generally it is preferable to maintain a 1:1 ratio for microcrystalline cellulose:lactose monohydrate.

Example 4

Hard gelatine capsule composition

Amount per capsule		Ingredient
25	mg	COX-2 inhibitor
37	mg	Microcrystalline cellulose
37	mg	Lactose anhydrate
1	mg	Magnesium stearate
1 capsule		Hard gelatin capsule

Capsule dose strengths of between 1 and 50 mg can be accomodated by varying total fill weight, and the ratio of the first three ingredients. Generally it is preferable to maintain a 1:1 ratio for microcrystalline cellulose:lactose monohydrate.

Example 5

Oral solution

Amount per 5mL		Ingredient
50	mg	COX-2 inhibitor
to 5 mL		with Polyethylene oxide 400

Example 6

Oral suspension

Amount per 5mL dose	Ingredient	
101	mg	COX-2 inhibitor
150	mg	Polyvinylpyrrolidone

Oral suspension

Amount per 5mL dose	Ingredient	
2.5	mg	Poly oxyethylene sorbitan monolaurate
10	mg	Benzoic acid
to 5 mL with sorbitol solution (70%)		

Suspension dose strengths of between 1 and 50 mg/5 ml can be accomodated by varying the ratio of the first two ingredients.

Example 7

Intravenous infusion

Amount per 200 mL dose	Ingredient	
1	mg	COX-2 inhibitor
0.2	mg	Polyethylene oxide 400
1.8	mg	Sodium chloride
to 200 mL		Purified water

Example 8 The Effect of COX-2 Inhibitors in a Rat Model of Bone Cancer pain

Adult female rats are given intra-tibial injections of MRMT-1 rat mammary gland carcinoma cells (3µl, 10^7 cells/ml). These animals gradually develop mechanical hyperalgesia, mechanical allodynia (skin sensitivity to non-noxious stimuli) and hind limb sparing, beginning on day 12-14 following cell injection. COX-2 inhibitors, 5-methyl-2-(2'-chloro-6'-

fluoroanilino)-phenylacetic acid (hereinafter referred to as COX189) (10 and 30 mg/kg p.o.) and valdecoxib (30 mg/kg p.o.) are administered as described below and the results obtained compared with vehcle treated controls.

Intra-tibial inoculation of MRMT-1 cells induces a time-dependent hypersensitivity in the ipsilateral limb, measured as a shift in body weight to the contralateral limb. The increase in weight-bearing difference between contralateral and ipsilateral paw (weight shift from the affected to the unaffected limb) is evident by day 14 post-inoculation and continues to increase until day 20.

The repeated administration of COX189 (10 and 30mg/kg, p.o.) from day 10 post-tumour cell inoculation significantly attenuates the weight-bearing difference on days 14, 17 and 20 measured 1 hour after drug administration. This effect is significant for COX189 on days 10, 14, 17 and 20 as well as for valdecoxib (30mg/kg, p.o.) on day 20. The doses chosen for COX189 and valdecoxib are comparable. Lower doses are not studied.

The effect is not dose-dependent, there is no difference between the effect of COX189 administered at doses of 10 and 30mg/kg. The treatments induces a progressive and long-lasting reduction in hypersensitivity, since the weight-bearing difference is also attenuated when measured 1h before the first daily treatment. This preventative effect reaches significant levels for all three treatments on days 14 and 17. There is no significant difference between the effects measured before and after COX189 administration on each day for any individual treatment.

There is pronounced mechanical allodynia in the ipsilateral paw (vehicle group) both to a punctuate stimulus (static allodynia) and to light stroking of the skin (dynamic allodynia) on day 20 post-inoculation. The repeated administration of COX189 (10 and 30mg/kg, p.o.) or valdecoxib (30mg/kg, p.o.) significantly reverses static allodynia on day 20, measured 90 minutes after the last administration. There is a tendency to reduce dynamic allodynia by all treatments, although this reduction only reaches statistical significance for COX189 at the highest dose (30mg/kg, p.o.).

Measurement of COX189 levels in serum of the same animals, taken 3 hours after administration on day 20, shows concentrations of mean±SEM:19.0±1.7μM and 59.9±3.9μM for COX189, 10 and 30mg/kg, respectively

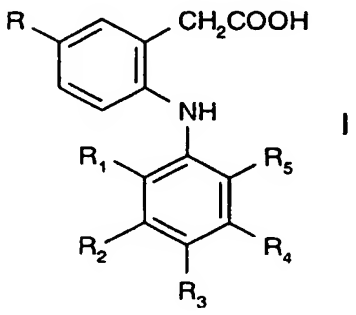
The levels of thromboxane B_2 in the samples from COX189-treated animals are 87.4±17.7%, 64.5±8.0% and 77.4±27.8% of the levels in the vehicle-control animals, for COX189 (10mg/kg), COX189 (30mg/kg) and valdecoxib (30mg/kg), respectively. These data indicate that COX-1 is not inhibited by these doses, implying that the benefits seen in the model are COX-2 as opposed to COX-1 derived.

In addition it is found in this animal model experiment that repeated administration of COX189 at 10 and 30mg/kg significantly inhibits the radiologically observed structural changes on day 20. COX189 at 30mg/kg is able to significantly inhibit the loss of bone mineral density compared to vehicle treated animals. Valdecoxib at 30mg/kg has no significant effect on either parameter.

CLAIMS

1. A method of treating cancer pain in a subject in need of such treatment which comprises administering to the subject an effective amount of a COX-2 inhibitor;

2. A method according to claim 1 in which the COX-2 inhibitor is a compound of formula I



I

wherein R is methyl or ethyl;

R_1 is chloro or fluoro;

R_2 is hydrogen or fluoro;

R_3 is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxy;

R_4 is hydrogen or fluoro; and

R_5 is chloro, fluoro, trifluoromethyl or methyl;

a pharmaceutically acceptable salts thereof; or

a pharmaceutically acceptable prodrug esters thereof..

3. Use of a compound of formula I as defined in claim 2 (or pharmaceutically acceptable salt or prodrug ester thereof) for the preparation of a medicament, for use in the treatment of cancer pain.

4. Use of a compound of formula I as defined in claim 2 (or pharmaceutically acceptable salt or prodrug ester thereof) for the treatment of cancer pain.

5. A package comprising a compound of formula I as defined in claim 2 (or pharmaceutically acceptable salt or prodrug ester thereof) together with instructions for use in the treatment of cancer pain.

6. A method according to claim 2, or use according to claim 3, in which the compound of formula I is 5-methyl-2-(2-chloro-6-fluoroanilino)-phenylacetic acid or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable prodrug ester thereof.

7. A method according to claim 1 or use according to clöaim 3, for the treatment of bone cancer pain.

8. A method according to claim 1 or use according to claim 3, in which the compound of formula I is in the form of an oral composition or an injectable composition.

9. A method for the inhibition of bone loss, advantageously in cancer, which comprises administering an effective amount of a COX-2 inhibitor of formula I (or an ester or prodrug thereof) as defined in claim 2 to a subject in need of such treatment.

10. Use of a COX-2 inhibitor of formula I (or an ester or prodrug thereof) as defined in claim 2, for the preparation of a medicament for the inhibition of bone loss, in particular bone loss in cancer.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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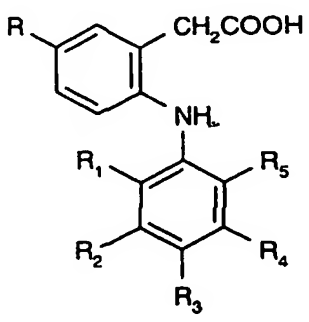
Published:
— *with international search report*

(88) Date of publication of the international search report:
1 April 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2003/090737 A3

(54) Title: METHODS AND COMPOSITIONS FOR TREATMENT OF CANCER PAIN



(I)

(57) Abstract: The invention provides a method of treating cancer pain, e.g. bone cancer pain, in a subject in need of such treatment which comprises administering to the subject an effective amount of a COX-2 inhibitor; advantageously a compound of formula (I); wherein R, R_1 R_2, R_3, R_4, and R_5 are as defined; a pharmaceutically acceptable salts thereof; or a pharmaceutically acceptable prodrug ester thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/04152

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/196 C07C229/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 32189 A (GAO DANCHEN ;SEARLE & CO (US); MAZHARY AHMAD M (US); HLINAK ANTHON) 8 June 2000 (2000-06-08)	1,7,8
Y	claim 1 page 5, line 20 - line 21 page 9, line 30 - line 32	1-8
X	WO 01 91750 A (HASSAN FRED ;BRUGGER ANDREW (US); FORBES JIM (US); GAO PING (US);) 6 December 2001 (2001-12-06)	1,7,8
Y	claim 1 * page 17, paragraph [0068] *	1-8
X	US 2002/013357 A1 (NADKARNI SREEKANT ET AL) 31 January 2002 (2002-01-31)	1,7,8
Y	claim 1 * page 1, paragraph [0004] * * page 3, paragraph [0049] *	1-8

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 July 2003	24. 11. 2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Beranová, P.

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 945 134 A (BOEHRINGER INGELHEIM PHARMA) 29 September 1999 (1999-09-29) claim 1	1-8
Y	WO 99 11605 A (NOVARTIS AG) 11 March 1999 (1999-03-11) claims 1,8	1-8
Y	MEDHURST S J ET AL: "A rat model of bone cancer pain." PAIN, vol. 96, no. 1-2, March 2002 (2002-03), pages 129-140, XP002249243 ISSN: 0304-3959 page 140, left-hand column, paragraph 3	1,7,8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/04152

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 9, 10
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-8

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 9, 10

Present claims 1, 7 and 8 relate to a compound defined by reference to a desirable characteristic or property, namely "COX-2 inhibitor". The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds of formula (I) and rofecoxib, etoricoxib, celecoxib, valdecoxib and parecoxib as indicated in the description (page 1, 5th paragraph).

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-8

The use of COX-2 inhibitors for the treatment of cancer pain

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2. claims: 9, 10

The use of COX-2 inhibitors for the treatment of bone loss

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 03/04152

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Information on patent family members

International Application No
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